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(71) Applicant *(for all designated States except US)*: **EMCURE PHARMACEUTICALS LTD** [IN/IN]; Ratilal Bhagwandas Estate, Dapodi, Pune 411 012 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MEHTA, Satish** [IN/IN]; Emcure Pharmaceuticals Ltd., Ratilal Bhagwandas Estate, Dapodi, Pune 411 012 (IN). **SHAH, Mahesh** [IN/IN]; Emcure Pharmaceuticals Ltd., Ratilal Bhagwandas Estate, Dapodi, Pune 411 012 (IN). **JOSHI, Manjusha** [IN/IN]; Emcure Pharmaceuticals Ltd., Ratilal Bhagwandas Estate, Dapodi, Pune 411 012 (IN). **KALE, Dhanashri** [IN/IN]; Emcure Pharmaceuticals Ltd., Ratilal Bhagwandas Estate, Dapodi, Pune 411 012 (IN).

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WO 01/85134 A1

(54) Title: PHARMACEUTICAL SOLID COMPOSITIONS AND PROCESS FOR THE PRODUCTION OF MOUTH DISSOLVING TABLETS

(57) Abstract: Solid pharmaceutical compositions containing various ingredients for the production of Mouth dissolving Tablets (MDT) are described. Also described herewith the process using the said compositions which when processed as per the process described herein produce tablets containing active pharmaceutical ingredients preferably the Non Steroid Analgesics. The compositions are prepared by spraying the granulating solution on the dry-mix consisting of polyalcohol and the active ingredient in fluidized bed dryer containing such spraying facility. The tablets prepared using the compositions described using the process show remarkable fast disintegration in the mouth cavity without any action like chewing, even in absence of any carrier like water or hot/cold drinks. The tablets being rapid disintegrating can be easily administered to the aged, children and non-cooperating patients.

TITLE OF INVENTION

PHARMACEUTICAL SOLID COMPOSITIONS AND PROCESS FOR THE PRODUCTION OF MOUTH DISSOLVING TABLETS

Field of invention

This invention relates to pharmaceutical compositions and a process for manufacturing rapid disintegrating tablets. More particularly it relates to the said composition containing a Non-steroid Anti Inflammatory Drugs (NSAIDs) such as Nimesulide and a process for manufacturing the tablets characterized by high disintegrating property in the buccal cavity, using the said pharmaceutical compositions.

Various types of preparations such as syrups, tablets, capsules, sustained release preparations are used to administer the active ingredient. Of all these oral drug administration methods, solid tablets or capsules are the most commonly used modes. Tablets are by far the most common and popular mode of drug administration. Various types of tablets are now known and available such as un-coated, film coated, sugar coated, chewable, sustained release etc.

Conventionally the tablets are administered along with water to pass through the buccal cavity or required to be chewed to disintegrate to release the active ingredient, which is absorbed in the body. The time in which the active ingredient of the tablet is available depends upon the type of the tablets and its disintegrating time.

Although the conventional tablets are by far the most commonly used mode of administration of the drugs, it has its own limitations. The administration of tablets become difficult in infants, minors and aged. The taste of the tablet, which is dependent mostly upon the active ingredient also, plays important role. Many bitter drugs need coating so as to avoid the experiencing the bitter or unpleasant taste.

Background Art

US patent no. 5,958,453, describes a solid pharmaceutical preparation with improved buccal disintegrating and dissolving properties. A solid pharmaceutical preparation comprising a pharmaceutically active ingredient,

erythritol, crystalline cellulose and a disintegrant, exhibiting fast buccal disintegrating/dissolving property has been provided. Although this patent mentions use of mannitol as one of the components of the pharmaceutical composition it is optional or in addition to erythritol.

US Patent no. 5,955,107 describes pharmaceutical suspension tablet composition comprising of a therapeutic amount of pharmaceutically active ingredient, croscaarmellose sodium, micro-crystalline cellulose and co-processed additives of consisting essentially of micro-crystalline cellulose and calcium, sodium alginate complex. However it does not disclose the composition and the preparation of tablets which have rapid disintegrating properties in the buccal cavity.

The PCT application no. 99/59544 describes orally disintegrating tablets, however they are coated with an enteric coating layer. The average particle diameter also is limited to 400.

Another PCT application no. WO99/55311 also describe tablets quickly disintegrating in oral cavity and a process for the producing the same. However the tablets described in this application are produced by wet granulating sugars highly soluble in water and swelling fillers together with crystalline cellulose.

Still another PCT application No. WO 99/47124 describes tablets quickly disintegrating in the oral cavity containing drug, saccharides and amorphous saccharides. In the said process the crystalline drug and the saccharides are converted into amorphous ones in pharmaceutically acceptable solvent. In the production of the said tablets the amorphous saccharides are irreversibly converted into crystalline ones after the step of drying under moistening.

The WO 99/32092 describes a method for the manufacture of tablets, which disperse easily and quickly in the oral cavity, however they necessarily need a bite for disintegration. These tablets also contain waxy material and phospholipid or an intense sweetener derived from fruit flavonoids.

Still another PCT application no. WO 99/04758 published on February 4, 1999 teaches a process for the preparation of a granulate suitable to the preparation of rapidly disintegrating mouth soluble tablets. The process

comprises granulating in a fluidized bed a polyalcohol and optionally other solid components selected for active principles, lubricants, sweetening agents, flavours with an aqueous solution or aqueous dispersion of a water soluble or water dispersible polymer.

The pharmaceutical compositions mentioned above have various limitations. They contain insoluble inorganic matters, which interfere with the disintegrated active ingredient in the buccal cavity. Others need presence of an aqueous solution or an aqueous dispersion of water-soluble polymer. Some of the formulations need to be prepared in pharmaceutically acceptable solvents. Still others need presence of swellable fillers with crystalline cellulose or waxy materials. It is therefore desirable to develop a formulation for the preparation of the tablets, which rapidly dissolve in the buccal cavity even without water. It is also desirable that such tablets should have pleasant, palatable and refreshing taste and aroma.

Conventionally the tablets are prepared by either dry or wet mixing of the solid or liquid ingredients such as pharmaceutically active component, additives, preservatives, flavours in a granulator, mixing thoroughly using conventional kneading process, drying the granules and compressing into tablets of desired shape, size and configuration.

The inventors of the present invention have observed that the processing a pharmaceutical composition comprising the active ingredient, a polyalcohol like mannitol, sweetening agents like sugars, artificial flavours and stabilizing agents for the production of tablets as per process described hereunder yield tablets having very fast disintegrating property in the buccal cavity. These tablets do not have other insoluble matters in the tablets in such quantities, which interfere with the disintegration of the tablets in the buccal cavity.

The main object of the present invention therefore is to provide an improved pharmaceutical composition useful for manufacture of solid preparations, particularly tablets, which rapidly disintegrate into the buccal cavity.

Another object is to provide compositions, which have negligible quantities of the insoluble ingredients thereby considerably reducing their interference with the disintegrated active ingredient.

Still another object is to provide compositions, which are independent of any water-soluble or water dispersible polymers, waxy materials or microcrystalline cellulose.

Yet another object is to provide an improved process for the manufacture of solid preparations, useful for preparation of rapid mouth disintegrating tablets using the pharmaceutical solid compositions described in the present invention.

Disclosure of the invention

Accordingly the present invention provides pharmaceutical solid compositions useful for preparing rapid mouth disintegrating tablets, having a general formula

$$A_{(x)}B_{(y)}C_{(z)}$$

Wherein A is a pharmaceutically active ingredient,

B is a polyalcohol

C is mixture of pharmaceutically acceptable colour, sweetener, buffering agent, disintegrating agent, and lubricant and pharmaceutically acceptable flavour.

X= 27 to 67% w/w of the tablet

Y= 13 to 58% w/w of the tablet

Z= 15 to 20 % w/w of the tablet

And X+Y+Z=100%

In one of the embodiments of the present invention the pharmaceutically active ingredient may be such as Non steroidal Analgesic or anti-inflammatory drug exemplified by Nimesulide, Piroxicam preferably Nimesulide.

In another embodiment the polyalcohol used may be mannitol, sorbitol or mixtures thereof, preferably mannitol.

In another embodiment the polysaccharide used may be maltose, glucose, sucrose, preferably maltose.

In yet another embodiment the pharmaceutically acceptable colouring agent may be Quinoline Yellow, sunset yellow, erythrosine, brilliant blue, preferably Quinoline yellow.

In still another embodiment the sweetener may be selected from pharmaceutically acceptable Aspartame, sodium saccharin, glycerizha powder or mixtures thereof, preferably Aspartame.

In yet another embodiment the buffering agent may be pharmaceutically acceptable Citric Acid, tartaric acid, or mixture thereof, preferably Citric Acid.

In yet another embodiment the disintegrating agent may be selected from pharmaceutically acceptable Crospovidone, sodium starch glycolate, croscarmellose, preferably Crospovidone.

In yet another embodiment the lubricant may be selected from pharmaceutically acceptable Stearate of magnesium, calcium or talc, preferably Magnesium Stearate.

In still another embodiment pharmaceutically accepted flavour may be selected from Trusil Lemon flavour, Trusil orange, Trusil mix fruit, Trusil pineapple, Trusil mint, or mixtures thereof, preferably Trusil Lemon flavours.

In another embodiment the concentration of the active ingredient may be 50 to 400 mg. /tablet

In still another embodiment the combined concentration of the polyalcohol and the polysaccharide may be in the range of 0.1 to 20% w/w of the tablet.

In yet another embodiment the concentration of the colouring agent may be 0.011 to 1.0% w/w of the tablet.

In still another embodiment the concentration of the sweetener may be 0.1 to 5.0% w/w of the tablet.

In another embodiment the concentration of buffering agent may be 1 to 6 % w/w of the tablet.

In still another embodiment the concentration of disintegrating agent may be 0.1 to 6.0 % w/w of the tablet.

In yet another embodiment the concentration of the lubricant may be 0.1 to 6.0% w/w of the tablet.

In still another embodiment the concentration of the flavour may be 0.1 to 5.0% w/w of the tablet.

In another embodiment, the present invention provides a process for the manufacture of rapid mouth disintegrating tablets using the abovementioned composition, which comprises preparing a granulating solution of a saccharide in pharmaceutically acceptable purified water, separately preparing a dry mix of polyalcohol, active ingredient and the pharmaceutically acceptable colouring agent, loading the said drymix in a fluidized bed granulator/processor, allowing the drymix to fluidize at a temperature ranging between 40 to 70°C, granulating the drymix by spraying the granulating solution on the dry mix, at the constant temperature in the range of 40 to 70 °C, drying the granulated mixture till the loss on drying of the said mixture is less than 1 to 2%, adding a mixture of buffering agent, disintegrating agent, lubricating agent and the desired pharmaceutically acceptable flavour to obtain the granulated mixture and preparing the tablets of desired shape using this granulated mixture by conventional compressing methods.

In a feature of the present invention the granulation and the drying is carried out simultaneously in the fluidized bed machines provided by Sapphire or Glatt.

The following examples describe the compositions of the present invention in details and the process for the preparation of tablets, which are illustrative only and should not be construed to limit the scope of the present invention in any manner whatsoever.

Example –1

Nimesulide 100 mg. tablets were prepared using following composition. Batch size: 1,00,000 tablets

Ingredient	**Concentration mg/tab**	**Quantity used per batch (kg.)**
Nimesulide	100.00	10.000
Mannitol*	187.00	18.700
Maltose	20.34	2.034

Quinoline Yellow Colour	0.30	0.030
Aspartame*	5.10	0.510
Citric Acid*	10.50	1.050
Crospovidone*	12.45	1.245
Magnesium Stearate*	5.25	0.525
Trusil Lemon Flavour	5.10	0.510

* The ingredients are pharmaceutically acceptable confirming to mandatory pharmacopoeia.

10.00 kg. of Nimesulide was pulverized through multimill. Mannitol 18.7 kg. was separately sifted through 40-mesh sieve. The dry mixture of prepared by mixing the Nimesulide, mannitol and Quinoline yellow 30.0 gm. The mixture was mixed thoroughly in a planetary mixer for 30 minutes. A granulating solution was prepared by dissolving 18.70 kg. of Mannitol in 2.0 lt. of boiled and cooled water. The granulating mixture was loaded in a fluidized bed dryer equipped with spraying mechanism and was allowed to fluidize at 40°C. The granulating solution was sprayed on the dry mix keeping the temperature constant till the entire granulating solution was exhausted. The granulated mixture so obtained was allowed to dry till the loss on drying was below 1%. A mixture of Crospovidone 1.245 kg., Aspartame 0.510 kg., Citric acid 1.050 kg., and Trusil lemon flavour 0.510 kg was sifted through 80 mesh. The above mixture was mixed with dried granulated mixture in a drum mixer for ten minutes and the tablets were prepared from the granulated mixture so obtained by compression method.

The disintegration time of the tablet as determined by disintegration method was 40 seconds.

The buccal cavity disintegration time as determined on adult sample was 35 seconds.

Example –2

Piroxicam 10 mg. tablets were prepared using following composition. Batch size:5000 tablets.

Ingredient	Concentration mg/tab	Quantity used per batch (gm.)
Piroxicam IP *	10.00	50.000
Mannitol IP*	187.00	935.00
Maltose	20.00	100.00
Sunset Yellow Colour	0.3	1.50
Aspartame IP*	5.70	28.5
Citric Acid IP*	10.50	52.50
Crospovidone USP*	12.50	62.50
Magnesium Stearate IP *	5.00	25.00
Trusil Mango Flavour	5.00	25.00
	256 mg/tab	

* The ingredients are pharmaceutically acceptable confirming to mandatory pharmacopoeia.

50.00 gm of Piroxicam & Mannitol 935 gm. were separately sifted through 40-mesh sieve. The dry mixture prepared by mixing the Piroxicam, mannitol was mixed thoroughly in a tub for 5 minutes. A granulating solution was prepared by dissolving 100.00 g. of Maltose & sunset yellow colour 1.5 g in 500 ml. of boiled and cooled water. The granulating mixture was loaded in a fluidized bed dryer/processor equipped with spraying mechanism and was allowed to fluidize at 40°C. The granulating solution was sprayed on the dry mix keeping the temperature constant till the entire granulating solution was exhausted. The granulated mixture so obtained was allowed to dry till the loss on drying was below 1%. A mixture of Crospovidone 62.50 g., Aspartame 28.5 g., Citric acid 52.50 g, Magnesium stearate 25.0 g and Trusil Mango flavour 25.0 g were sifted through 80 mesh. The above mixture was mixed with dried granulated mixture in a tub for 5 minutes and the tablets were prepared from the granulated mixture so obtained by compression method.

The disintegration time of the tablet as determined by using disintegration test apparatus was 40 seconds.

The buccal cavity disintegration time as determined on adult sample was 45 seconds.

Example –3

Nimesulide 50 mg. tablets were prepared using following composition. Batch Size:10,000 tablets.

Ingredient	**Concentration mg/tab**	**Quantity used per batch (gm.)**
Nimesulide	50.00	500.000
Mannitol*	115.00	1150.00
Maltose	11.00	110.0
Quinoline Yellow Colour	0.175	1.750
Aspartame*	2.50	25.000
Citric Acid*	6.50	65.000
Crospovidone*	8.830	88.30
Magnesium Stearate*	3.00	30.000
Trusil Lemon Flavour	3.00	30.000
	200 mg/tab	

* The ingredients are pharmaceutically acceptable confirming to mandatory pharmacopoeia.

500.00 gm. of Nimesulide, Mannitol 1150 gm & Quinoline yellow colour 1,750 gm. were separately sifted through 40-mesh sieve. The dry mixture prepared by mixing the Nimesulide, mannitol & Quinoline yellow . The mixture was mixed thoroughly in a tub for 5 minutes. A granulating solution was prepared by dissolving 110.00 g. of Maltose in 500 ml. of boiled and cooled water. The granulating mixture was loaded in a fluidized bed dryer/processor equipped with spraying mechanism and was allowed to

fluidize at 40°C. The granulating solution was sprayed on the dry mix keeping the temperature constant till the entire granulating solution was exhausted. The granulated mixture so obtained was allowed to dry till the loss on drying was below 1%. A mixture of Crospovidone 88.30 g., Aspartame 25.0 g., Citric acid 65.00 g, Magnesium stearate 30.0 g and Trusil Lemon flavour 30.0 g were sifted through 80 mesh. The above mixture was mixed with dried granulated mixture in a tub for 5 minutes and the tablets were prepared from the granulated mixture so obtained by compression method.

The disintegration time of the tablet as determined by using disintegration test apparatus was 50 seconds.

The buccal cavity disintegration time as determined on adult sample was 35 seconds.

Example –4

Nimesulide 50 mg. tablets were prepared using following composition. Batch Size :10,000 tablets.

Ingredient	**Concentration mg/tab**	**Quantity used per batch (gm.)**
Nimesulide	50.00	500.000
Mannitol*	115.00	1150.00
Maltose	11.00	110.00
Quinoline Yellow Colour	0.175	1.750
Aspartame*	2.50	25.000
Citric Acid*	6.50	65.000
Sodium Starch Glycolate [Primojel]*	10.830	108.30
Magnesium Stearate*	3.00	30.000
Trusil Lemon Flavour	3.00	30.000
	202 mg/tab	

*The ingredients are pharmaceutically acceptable confirming to mandatory pharmacopoeia.

500.00gm of Nimesulide , Mannitol 1150 gm & Quinoline yellow colour 1.750 gm. were separately sifted through 40-mesh sieve. The dry mixture prepared by mixing the Nimesulide, mannitol & Quinoline yellow. The mixture was mixed thoroughly in a tub for 5 minutes. A granulating solution was prepared by dissolving 110.00 g. of Maltose in 500 ml. of boiled and cooled water. The granulating mixture was loaded in a fluidized bed dryer equipped with spraying mechanism and was allowed to fluidize at 40°C. The granulating solution was sprayed on the dry mix keeping the temperature constant till the entire granulating solution was exhausted. The granulated mixture so obtained was allowed to dry till the loss on drying was below 1%. A mixture of Sodium Starch Glycolate IP [Primojel] 108.30 g., Aspartame 25.0 g., Citric acid 65.00 g, Magnesium stearate 30.0 g and Trusil Lemon flavour 30.0 g were sifted through 80 mesh. The above mixture was mixed with dried granulated mixture in a tub for 5 minutes and the tablets were prepared from the granulated mixture so obtained by compression method.

The disintegration time of the tablet as determined by using disintegration test apparatus was 35 seconds.

The buccal cavity disintegration time as determined on adult sample was 30 seconds.

Example –5

Nimesulide 50 mg. tablets were prepared using following composition. Batch Size: 10,000 tablets

Ingredient	**Concentration mg/tab**	**Quantity used per batch (gm.)**
Nimesulide	50.00	500.000
Mannitol*	115.00	1150.00
Maltose	11.00	110.00
Quinoline Yellow Colour	0.175	1.750
Aspartame*	2.50	25.000

Tartaric Acid*	8.00	80.000
Sodium Starch Glycolate [Primojel]*	10.830	108.30
Magnesium Stearate*	3.00	30.000
Trusil Lemon Flavour	3.00	30.000
	202 mg/tab	

*The ingredients are pharmaceutically acceptable confirming to mandatory pharmacopoeia.

500.00gm of Nimesulide, Mannitol 1150 gm & Quinoline yellow colour 1.750 gm. were separately sifted through 40-mesh sieve. The dry mixture prepared by mixing the Nimesulide, mannitol & Quinoline yellow. The mixture was mixed thoroughly in a tub for 5 minutes. A granulating solution was prepared by dissolving 110.00 g. of Maltose in 500 ml. of boiled and cooled water. The granulating mixture was loaded in a fluidized bed dryer equipped with spraying mechanism and was allowed to fluidize at 45°C. The granulating solution was sprayed on the dry mix keeping the temperature constant till the entire granulating solution was exhausted. The granulated mixture so obtained was allowed to dry till the loss on drying was below 1%. A mixture of Sodium Starch Glycolate IP [Primojel] 108.30 g., Aspartame 25.0 g., Tartaric acid 80.00 g, Magnesium stearate 30.0 g and Trusil Lemon flavour 30.0 g were sifted through 80 mesh. The above mixture was mixed with dried granulated mixture in a tub for 5 minutes and the tablets were prepared from the granulated mixture so obtained by compression method.

The disintegration time of the tablet as determined by using disintegration test apparatus was 40 seconds.

The buccal cavity disintegration time as determined on adult sample was 35 seconds.

The main advantages of the present invention are as follows:

1. The composition provided by the present invention for preparation of the tablets contains almost negligible quantities of inorganic insoluble material thereby giving pleasant feeling in the buccal cavity during disintegration of the tablets.
2. The tablets do not require any chewing or water or any other drink for administration of the tablets. This is useful for administrating the drug to the aged or infants and un-cooperating patients.
3. The composition does not contain any polymers, wax or any other substances.
4. The disintegrating time of the tablets being very less, rapid bio-availability of the active ingredient is achieved, which is essential in case of analgesics.
5. The process provided by the present invention ensures uniform granulation as the granulation and drying is done simultaneously by spraying the granulating material on the dry mix.

CLAIMS

1. Pharmaceutical solid compositions useful for preparing rapid mouth disintegrating tablets, having a general formula

$$A_{(x)}B_{(y)}C_{(z)}$$

Wherein A is a pharmaceutically active ingredient,

B is a polyalcohol

C is mixture of pharmaceutically acceptable colour, sweetener, buffering agent, disintegrating agent, lubricant and pharmaceutically acceptable flavour.

X= 27 to 67% w/w of the tablet

Y= 13 to 58 % w/w of the tablet

Z= 15 to 20 % w/w of the tablet and X+Y+Z=100%

2. A composition as claimed in claim 1 wherein the pharmaceutically active ingredient may be such as Non steroidal Analgesic or anti inflammatory drug exemplified by Nimesulide, Piroxicam preferably Nimesulide.

3. A composition as claimed in claim 1, wherein the polyalcohol used may be mannitol, sorbitol or mixtures thereof, preferably mannitol.

4. A composition as claimed in claim 1 to 2, wherein the polysaccharide used may be maltose, glucose, sucrose, preferably maltose.

5. A composition as claimed in claims 1 to 3, wherein the pharmaceutically acceptable colouring agent may be Quinoline Yellow, sunset yellow, erythrosine, brilliant blue, preferably Quinoline yellow.

6. A composition as claimed in claims 1 to 4, the sweetener may be selected from pharmaceutically acceptable Aspartame, sodium saccharin, glycerizha powder or mixtures thereof, preferably Aspartame.

7. A composition as claimed in claims 1 to 5, wherein the buffering agent may be pharmaceutically acceptable Citric Acid, tartaric acid, or mixture thereof, preferably Citric Acid.

8. A composition as claimed in claims 1 to 6, wherein the disintegrating agent may be selected from pharmaceutically acceptable Crospovidone, sodium starch glycollate, croscarmellose, preferably Crospovidone.

9. A composition as claimed in claims 1 to 7, wherein the lubricant may be selected from pharmaceutically acceptable Stearate of magnesium, calcium or talc, preferably Magnesium Stearate.

10. A composition as claimed in claims 1 to 8, wherein pharmaceutically accepted flavour may be selected from Trusil Lemon flavour, Trusil orange, Trusil mix fruit, Trusil pineapple, Trusil mint, or mixtures thereof, preferably Trusil Lemon flavour.

11. A composition as claimed in claims 1 to 9, wherein the concentration of the active ingredient may be 50 to 400 mg./tablet

12. A composition as claimed in claims 1 to 10, wherein the combined concentration of the polyalcohol and the polysaccharide may be in the range of 0.1 to 20% w/w of the tablet.

13. A composition as claimed in claims 1 to 11, wherein the concentration of the colouring agent may be 0.011 to 1.0% w/w of the tablet.

14. A composition as claimed in claims 1 to 12, wherein the concentration of the sweetener may be 0.1 to 5.0% w/w of the tablet.

15. A composition as claimed in claims 1 to 13, wherein the concentration of buffering agent may be 1 to 6 % w/w of the tablet.

16. A composition as claimed in claims 1 to 14, wherein the concentration of disintegrating agent may be 0.1 to 6.0% w/w of the tablet.

17. A composition as claimed in claims 1 to 15, wherein the concentration of the lubricant may be 0.1 to 6.0% w/w of the tablet.

18. A composition as claimed in claims 1 to 16, wherein concentration of the flavour may be 0.1 to 5.0% w/w of the tablet.

19. A process for the manufacture of rapid mouth disintegrating tablets using composition claimed in claim 1, which comprises preparing a granulating solution of a saccharide in pharmaceutically acceptable purified water, separately preparing a dry mix of polyalcohol, active ingredient and the pharmaceutically acceptable colouring agent, loading the said drymix in a fluidized bed dryer, allowing the drymix to fluidize at a temperature ranging between 40 to 70°C, granulating the drymix by spraying the granulating solution on the dry mix, at the constant temperature in the

range of ambient 40 to 70 °C, drying the granulated mixture till the loss on drying of the said mixture is less than 1%, adding a mixture of buffering agent, disintegrating agent, lubricating agent and the desired pharmaceutically acceptable flavour to obtain the granulated mixture and preparing the tablets of desired shape using this granulated mixture by conventional compressing methods.

20. Pharmaceutical solid compositions useful for preparing rapid mouth disintegrating tablets as dully described hereinabove with reference to the examples contained therein.

INTERNATIONAL SEARCH REPORT

Interna : Application No
PCT/IN 00/00055

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 99 04758 A (ELAN) 4 February 1999 (1999-02-04) claims 1,2,5,6 page 12; example 2 page 5, line 28 -page 6, line 13 page 9, line 25 -page 10, line 4	1-4,6-9, 11-20 10
Y	WO 98 52541 A (WARNER-LAMBERT) 26 November 1998 (1998-11-26) claims 1,3,5 tables 1-6	10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/IN 00/00055

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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